

REMARKS

As a preliminary matter, Applicants thank the Examiner for courtesies extended to Applicants' representatives, the undersigned, Dr. Laura Heisler and Dr. Victoria Sutton, during the telephonic interview of October 19, 2006. The rejections of record and possible amendments to overcome them were discussed. Applicants thank the Examiner for suggesting the amended claim language regarding 72% sequence identity.

By the present communication, claims 40, 45, 46, 47, and 60 are amended, and claims 61-72 are added to define Applicants' invention with greater particularity. No new matter has been added and the new claims are fully supported by the specification and claims as originally filed. In particular, support may be found at, but not limited to, page 7, lines 9-23, page 17, lines 14-23. Claims 29, 37, 40-48, and 59-72 are pending. Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

I. Claim Rejections Under 35 U.S.C. § 112, second paragraph

Claims 40, 41, 46-48, 59 and 60 stand rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite because "it is unclear as to what is encompassed by the referred to 'conservative amino acid variant of SEQ ID NO: 4.'" Office Action, p. 2. Applicants respectfully traverse this rejection.

Applicants draw the Examiner's attention to page 7, lines 9 – 29, of the specification where the meaning of the phrase "conservative amino acid variant" is discussed at length. Consistent with the meaning known in the art, the phrase is described in general terms (e.g., "an alkyl amino acid is substituted for an alkyl amino acid... an aromatic amino acid is substituted for an aromatic amino acid," etc.) and exemplified by substitutions of amino acids in various groups (e.g., phenylalanine, tyrosine, and tryptophan are interchangeable). Moreover, as amended, independent claims 40, 46, and 47 each recite that the variants have "one or more

conservative amino acid substitutions to about 72% sequence identity to SEQ ID NO: 4,” allowing the skilled artisan to determine exactly how many and what type of variants are permitted. (New claims 67-72 do not use the term “conservative variant.”) Accordingly, Applicants submit that claims 40, 41, 46-48, 59 and 60 as well as new claims 61-72 are clear as written and request that this ground of rejection be withdrawn.

II. Claim Rejections Under 35 U.S.C. § 112, first paragraph

A. Written Description

Applicants respectfully traverse the rejection of claims 40, 41, 46-48, 59 and 60 under 35 U.S.C. § 112, first paragraph as allegedly lacking adequate written description for “any conservative amino acid variant of SEQ ID NO: 4.” Independent claims 40, 46 and 47 recite that the conservative variant has one or more conservative amino acid substitutions to about 72% sequence identity to SEQ ID NO: 4, and new claims 67 and 70 recite that the amino acid variants have at least 72% sequence identity to SEQ ID NO: 4. Moreover, new claims 61, 63, 65, 69, and 72 recite variants of SEQ ID NO: 4 having a single amino acid substitution. As such, the amended and new claim language overcomes the present rejection for the reasons that follow.

Applicants respectfully submit that in view of the description in the application of conservative amino acid substitutions and the eight disclosed sequences of lysine 2,3-aminomutases, the person of ordinary skill in the art would recognize the inventors as being in possession of the claimed invention. First, as amended, claims 40, 46 and 47 do not recite all variants of SEQ ID NO: 4, but include only those conservative amino acid variants having one or more conservative amino acid substitutions to about 72% sequence identity to SEQ ID NO: 4. As noted above in section I, the meaning of “conservative amino acid variant” will be clear to the skilled artisan in view of the extensive discussion of the phrase on page 6, line 31 – page 7, line 27 of the application. Moreover, the number of conservative substitutions is spelled out: one or more down to 72% identity to SEQ ID NO: 4. Based on this discussion and the present

amendment, the skilled artisan will readily understand the limited number and types of substitutions encompassed by the claimed methods.

Accordingly, in view of the skill in the art and the understanding of sequence alignments of the disclosed enzyme species, including SEQ ID NO:4, Applicants have demonstrated adequate written description of the claimed methods using conservative amino acid variants of SEQ ID NO:4 having one or more conservative amino acid substitutions to about 72% sequence identity to SEQ ID NO:4. Applicants therefore respectfully request withdrawal of the rejection of claims 40, 41, 46-48, 59 and 60 under 35 U.S.C. § 112, first paragraph.

Second, in response to the assertion in the Office Action that the specification “fails to describe additional representative species of those conservative variants,” Applicants note that the eight widely divergent sequences of lysine 2,3-aminomutase disclosed in the specification offer the skilled artisan a wealth of information on amino acid substitutions which are tolerated by the enzyme. The fact that SEQ ID NO: 4 shares only 31% sequence homology with lysine 2,3-aminomutase from *Clostridia* as described on page 16 of the specification immediately alerts the skilled artisan to the wide tolerance many amino acid positions in the sequence have for modification. Indeed, the skilled artisan may readily compare the eight disclosed polypeptide sequences by inspection or through well-known techniques of sequence alignment (available at the time of filing and discussed in the next section) and identify positions where conservative amino acid substitutions may be made. In view of this information about the tolerance of the lysine 2,3-aminomutases to substitution, Applicants were well in possession of the claimed variants for claims 40, 46, and 47 as well as new claims 67 and 71.

Furthermore, Applicants respectfully submit that new claims 61-66, 69 and 72 are fully supported by the application as filed because they recite the use of lysine 2,3-aminomutase having SEQ ID NO:4 or a variant thereof having only a single amino acid substitution (claims 69 and 72) or a single conservative amino acid substitution (claims 61, 63, and 65). Because the present application describes conservative variants at length (see above discussion) and because the skilled artisan will readily be able to gauge which positions in SEQ ID NO: 4 are most

amenable to substitution (see above discussion), conservative or otherwise, it is clear that variants of SEQ ID NO: 4 having only a single amino acid substitution are well within the skill in the art. Accordingly, Applicants submit that they were in possession of the subject matter of claims 61-66, 69 and 72 at the time the application was filed.

As a final matter, Applicants respectfully submit that the amended claim language reciting that the conservative variant has one or more conservative amino acid substitutions to about 72% sequence identity to SEQ ID NO: 4 finds basis in the application as filed. Similarly, the claim language in new claims 67 and 70 reciting that the conservative variant has at least 72% sequence identity to SEQ ID NO: 4 also finds basis in the application as filed. There is no in haec verba requirement for written description so long as newly added claim limitations are supported in the specification through express, implicit, or inherent disclosure. Support for the amendment of claims 40, 46 and 47 and new claims 67 and 70 may be found throughout the specification. For example, at page 7, lines 9-23, it is explained that variants of lysine 2,3-aminomutases such as the clostridial enzyme “can be produced that contain conservative amino acid changes, compared with the parent enzyme.” That is, “variants can be obtained that contain one or more amino acid substitutions.” Thus, clearly variants of, e.g. SEQ ID NO: 2, and therefore other lysine 2,3-aminomutases disclosed therein, are contemplated which have less than 100% sequence identity. Indeed, as pointed out on page 17, lines 14-23, the eight disclosed sequences have up to about 72% sequence identity with the clostridial enzyme, and SEQ ID NO: 4 itself has only about 31%. The eight disclosed sequences therefore show that quite low amounts of sequence identity can be tolerated in this class of enzymes and provide basis for sequence identity down to 72% or at least 72% of SEQ ID NO: 4.

B. Enablement

Applicants respectfully traverse the rejection of claims 40, 41, 46-48, 59 and 60 under 35 U.S.C. § 112, first paragraph as allegedly lacking enablement because “the scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the

extremely large numbers of variants broadly encompassed by the claims, including any conservative amino acid variant of SEQ ID NO: 4.” Office Action, p. 5.

As amended, the rejected claims are directed to those conservative amino acid variants of SEQ ID NO: 4 which have one or more conservative amino acid substitutions to about 72% sequence identity to SEQ ID NO: 4. Moreover new claims 61-66 recite either a single conservative amino acid substitution or no such substitutions, and new claims 69 and 72 recite a single amino acid substitution. Hence the new and amended claims are not directed to all amino acid variants of SEQ ID NO: 4, but only a limited number of variants that are well within the ordinary skill in the art.

Also as noted above in Section II.A., the application provides copious guidance with respect to the nature of conservative amino acid substitutions and the tolerance of various positions in the amino acid sequence of SEQ ID NO: 4 for such substitutions. Applicants respectfully submit that the specification as read by the person of ordinary skill, establishes the four relationships discussed on page 6 of the Office Action at lines 4-11 as being relevant to avoid extended experimentation.

First, as noted above, the 31% sequence homology of SEQ ID NO: 4 with the lysine 2,3-aminomutase from *Clostridia* demonstrates the extreme tolerance which this enzyme generally has towards amino acid substitutions at many positions.

Second, it was well within the skill in the art at the time the application was filed to determine which regions of SEQ ID NO: 4 are most tolerant of modification based on the disclosed sequences of eight lysine 2,3-aminomutases. As confirmation, Applicants submit the Declaration of Dr. Victoria Sutton which shows an alignment of the disclosed sequences using standard techniques similar to or the same as those available at the time the application was filed. Dec., ¶ 3. The Appendix shows the alignment at each position of the clostridial enzyme as follows. The first column lists each amino acid position in the clostridial lysine 2,3-aminomutase enzyme, and the second column lists the clostridial amino acid at that position.

The third column shows each counterpart amino acid in the seven other lysine 2,3-aminomutase sequences for each clostridial position; dashes indicate the absence of a counterpart amino acid. The final column shows the percent sequence identity among all eight sequences. Dec., ¶ 4.

Thus, contrary to the assertion that the application fails to provide a rational and predictable scheme for modifying any amino acid residue of SEQ ID NO: 4, Applicants note that alignments of the eight disclosed sequences show exactly which residues appear to be the most and least tolerant of substitution. For example, positions 48-52, 54-58, 87-95, 140-152, 15-217, 267-270, and 373-382 have low sequence identity, indicating a likely tolerance for amino acid substitutions. Dec., ¶ 5. At the opposite end of the spectrum, residues 124, 128, 129, 131, and 133 are all 100% conserved and are unlikely to tolerate even a conservative amino acid substitution well. *Id.*

Finally, the choices of amino acid substitutions are not infinite as alleged in the Office Action because of the finite claim language. As amended, independent claims 40, 46 and 47 recite conservative amino acid variants of SEQ ID NO: 4 having one or more conservative amino acid substitutions to about 72% sequence identity to SEQ ID NO: 4, a high level of sequence identity. Moreover, the specification describes in detail what constitutes a conservative amino acid substitution. By their nature, conservative amino acid substitutions are inherently more likely to be tolerated than non-conservative substitutions. In conjunction with knowledge of which positions of SEQ ID NO: 4 are most likely to tolerate modification based on inspection of the eight disclosed sequences, the skilled artisan faces a far more limited array of rational choices than asserted in the Office Action.

Accordingly, because the skilled artisan understands how to make amino acid substitutions in the polypeptide of SEQ ID NO: 4 and which such substitutions are likely to be successful or unsuccessful based on information gleaned from the eight disclosed sequences and the skill in the art, Applicants submit that claims 40, 41, 46-48, 59 and 60 are enabled. As such, Applicants respectfully request withdrawal of this ground of rejection.

III. Conclusion

In view of the above amendment and remarks, reconsideration and favorable action on all claims are respectfully requested. If any issue remains to be resolved in view of this response, the Examiner is invited to contact the undersigned at the telephone number set forth below so a prompt disposition of this application can be achieved.

Respectfully submitted,

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